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Processes Underlying Sleep Regulation

Key Words

Sleep regulation
Sleep homeostasis
Slow-wave activity
Sleep spindles
EEG topography

Abstract

Sleep is regulated by homeostatic, circadian and ultradian processes. Slow waves and sleep spindles are EEG markers of sleep processes which have counterparts at the cellular level. The interaction of homeostatic and circadian sleep regulation has been formalized in the two-process model and validated in experiments. Sleep is not only a global brain phenomenon but also a regional cerebral process whose intensity may be influenced by prior activity during waking.

The regulatory processes underlying the manifestation of sleep and the release of hormones exhibit similarities. These include: (1) a sleep-waking dependent component of non-rapid-eye movement (nonREM) sleep intensity of which EEG slow-wave activity (SWA) is a reliable marker, and the release of growth hormone which occurs preferentially during deep nonREM sleep [1]; (2) a clock-like circadian process which is largely independent of sleep and waking, and which modulates both the nonREM/REM sleep ratio and hormones such as cortisol and melatonin [2], and (3) an ultradian process which is responsible for the alternation of the two basic sleep states nonREM sleep and REM sleep, which is associated with a variation of renin release [3].

Two-Process Model and SWA

The two-process model of sleep regulation posits that a homeostatic process (Process S) rises during waking and declines during sleep, and interacts with a circadian process (Process C) that is independent of sleep and waking

[4-6]. The time course of the homeostatic variable S was derived from EEG SWA. Under physiological conditions, this EEG variable constitutes an index of 'sleep intensity' which changes as a function of prior sleep and waking. Sleep deprivation enhances SWA and this enhancement depends on duration of waking [7, 8]. 'Sleep pressure' is not only augmented by sleep deprivation but reduced by daytime naps. According to the two-process model, the sum of cumulated SWA during the nap and the post-nap sleep episode is equal to the cumulated value of the baseline sleep episode. This prediction was confirmed in recent studies [9, 10].

Sleep spindles, another salient feature of the nonREM sleep EEG, can be measured by 'spindle frequency activity' (SFA; spectral power density in the 12-15 Hz band). Unlike SWA, SFA does not decrease during nocturnal sleep and, on average, shows an increasing trend. High values are seen at the onset and termination of nonREM sleep episodes. The dynamics of SFA show both a sleep-dependent and a circadian component [11, 12] and exhibit a complex relationship to SWA [12-16].

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Origin of EEG Slow Waves and Spindles

Recently, slow waves and sleep spindles were shown to be closely related to cellular changes at the level of thalamic and cortical neurons. The progressive hyperpolarization of thalamocortical neurons during sleep induces fluctuations in the membrane potential in the frequency range of the sleep EEG. Oscillations in the membrane potential of thalamocortical neurons occur in the range of sleep spindles when an intermediate level of hyperpolarization prevails, whereas fluctuations in the delta range are seen when the level of hyperpolarization is high [17–19]. Synchronized network oscillations were demonstrated to cease spontaneously at least in part through the persistent activation of a hyperpolarization-activated cation conductance [20]. The oscillations at the neuronal level are associated with corresponding changes in the EEG. Thus the progressive hyperpolarization of thalamocortical neurons after sleep onset [21] may account for the presence of SFA in the initial part of a nonREM sleep episode and for the predominance of slow waves in the middle portion [13, 14]. This progression of changes is enhanced when sleep pressure is high [14, 22] and is retarded when sleep pressure is reduced [10]. Recently, a slow component (<1 Hz) observed at the cellular level [23–25] was also identified in the sleep EEG [26]. Taken together these new developments indicate that sleep homeostasis can be investigated concomitantly at the microscopic level of neuronal membranes and at the macroscopic level of the EEG.

Independence and Interaction of Process S and C

Several lines of evidence point to the independent regulation of the homeostatic and circadian facet of sleep. Thus, rats rendered arrhythmic by lesions of the supra-chiasmatic nuclei maintained their ability to respond to sleep loss by a rise in SWA and REM sleep [27–29]. Recent experiments in the same species demonstrated that animals exposed to different photoperiods showed dramatic changes in the 24-hour distribution of sleep and waking while nonREM sleep homeostasis remained unaffected [30]. Similar results were obtained in the chipmunk [31] and the Djungarian hamster [32]. Finally, strong support for the basic assumptions of the two-process model has been obtained from human forced desynchrony experiments in which the homeostatic and circadian facet of sleep could be separately analyzed. In this protocol, subjects were scheduled to a 28-hour sleep-waking cycle [11, 33]. During one third of the cycle the lights were off and

the subjects were encouraged to sleep. Since under these experimental conditions the free-running circadian rhythm has a period of 24.1–24.2 h [34], the sleep episodes occurred at different circadian phases. The data showed that sleep propensity was at the maximum when the circadian rhythm of rectal temperature was at the minimum. Sleep propensity gradually decreased on the rising limb of the rectal temperature rhythm and reached the minimum 16 h after the temperature minimum. This phase corresponds to the habitual bedtime under entrained conditions. When sleep was initiated at this phase, sleep continuity was high. In contrast, poor sleep continuity was observed when sleep was initiated after the temperature minimum.

In accordance with the basic assumption, SWA, the marker of Process S, was shown to be determined mainly by homeostatic (i.e. sleep-waking dependent) factors, whereas REM sleep (or rather the REM sleep/nonREM sleep ratio) depended on both homeostatic and circadian factors. Furthermore, a previously postulated sleep-related inhibition of REM sleep [4] was confirmed by the results of the forced desynchrony study. The data from these experiments also showed that not only the timing of sleep but also the changes in daytime vigilance are governed by the interaction of Process S and C. The rising homeostatic sleep pressure during waking is compensated by the declining circadian sleep propensity [5, 35–37]. Conversely, during sleep the rising circadian sleep propensity may serve to counteract the declining homeostatic sleep pressure, thereby ensuring the maintenance of sleep.

Sleep – A Local Use-Dependent Process?

Although it has been clearly demonstrated that the level of SWA is determined by the duration of prior wakefulness, the physiological significance of this relationship and the underlying mechanisms are still obscure. Recently, the question arose whether sleep represents a global or a local brain process. The observations that the dolphin does not exhibit deep slow wave sleep in both hemispheres simultaneously, and that the selective deprivation of unihemispheric sleep gives rise to a unihemispheric slow wave sleep rebound [38], shows that the sleep process is not necessarily present in the entire brain. Two hypotheses were advanced which both imply that regional increases of neuronal activity and metabolic demand during wakefulness may result in selective changes in EEG synchronization of these neuronal populations during non-REM sleep [39, 40]. Benington and Heller [40] proposed

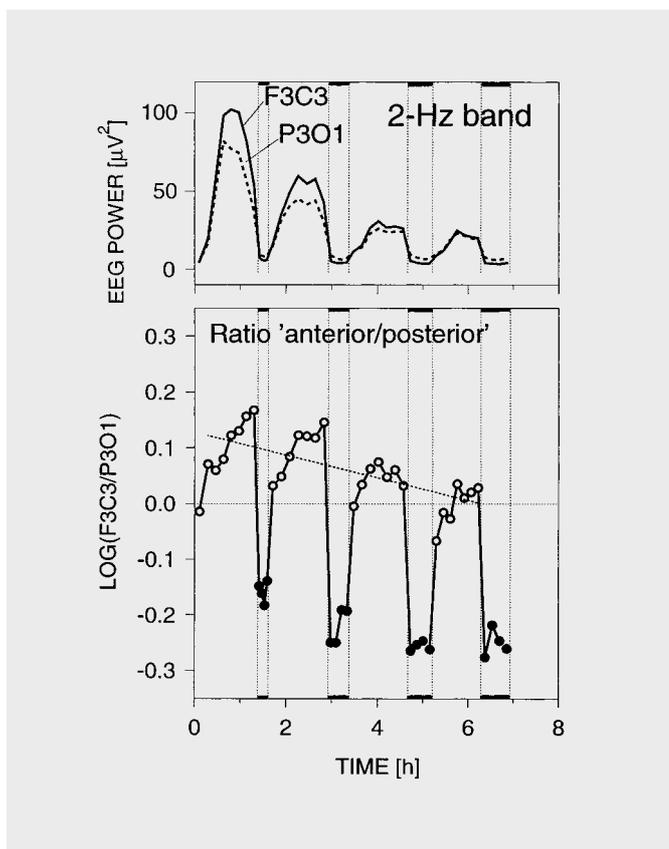


Fig. 1. Time course of EEG power during sleep in the 2-Hz bin (upper panel) for the anterior (F3-C3) and posterior (P3-O1) derivation, and of the corresponding log-transformed ratio (lower panels). Mean values ($n = 20$ subjects; 34 nights). Individual nonREM sleep episodes were subdivided into 7 equal intervals, REM sleep episodes into 4 intervals, and the time between lights-off and sleep onset was represented as 1 interval. Data were aligned with respect to sleep onset (cycle 1) or with respect to the first occurrence of stage 2 after a REM sleep episode (cycles 2–4). REM sleep is indicated by horizontal black bars at the top and bottom. Linear regression lines across nonREM sleep episodes are plotted for 2- and 6-Hz ratio plots (7 values per episode; $p < 0.05$) [modified from 47].

that adenosine, which is released upon increased metabolic demand via facilitated transport by neurons and glia cells throughout the CNS, promotes slow EEG potentials. Thus a use-dependent, local mechanism would underlie the sleep-deprivation-induced changes in the sleep EEG. Recent results support this notion. They include the sleep-inducing effect of adenosine agonists administered by intracerebroventricular [41] or subarachnoidal infusion [42] as well as the attenuation of the waking-induced increase of SWA by the adenosine antagonist caffeine in the rat [43] and human [44, 45].

The tenet of a local, use-dependent increase of sleep intensity was tested by investigating whether a local activation of a particular brain region during wakefulness affects the EEG recorded from the same site during sleep [46]. An intermittent vibratory stimulus was applied to the left or right hand during the 6-hour period prior to sleep to activate the contralateral somatosensory cortex. Stimulation of the right (dominant) hand resulted in a shift of power in the nonREM sleep EEG towards the left hemisphere. This effect was most prominent in the delta range, was limited to the first hour of sleep and was restricted to the central derivation situated over the somatosensory cortex. Finally, a recent topographical study revealed a sleep-dependent hyperfrontality of SWA which varies in the course of sleep [47, 48]. Thus in the initial two nonREM sleep episodes, the power in the 2-Hz band was dominant at the frontal derivation, whereas in the second part of sleep the anteroposterior gradient vanished (fig. 1). This finding is consistent with the notion that the sleep process may occur in a topographically graded manner by involving preferentially those neuronal populations that have been most activated during waking. It could be speculated that the progressive anteroposterior shift in power in the low-frequency range reflects a high 'need of recovery' in frontal parts of the cortex which seem to exhibit the largest activity during wakefulness [49]. Experiments involving a specific manipulation of daytime activity are required to test this possibility. In the framework of the two-process model, the results indicate that Process S declines in the anterior region of the brain at a steeper rate than in posterior regions and that therefore the homeostatic nonREM sleep-regulating process may exhibit regional differences. The concept of local aspects of sleep has considerable implications for the study of cerebral mechanisms which are involved in the control of hormonal changes.

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